

WHAT IS CLAIMED IS:

1 1. A method of making probe-chips comprising the steps of:
2 forming a plurality of probe arrays on a substrate;
3 separating said substrate into a plurality of chips, each of said chips comprising at
4 least one probe array thereon; and
5 mating at least one of said chips to a package, said package comprising a reaction
6 chamber, said reaction chamber comprising inlets for flowing fluid therein, said at least one
7 probe array in fluid communication with said reaction chamber.

1 2. The method as recited in claim 1 wherein said package is made by the steps
2 of:
3 injection molding first and second halves of said package; and
4 mating said first and second halves together.

1 3. The method as recited in claim 2 wherein one of said halves comprises flow
2 channels therein, said flow channels in communication with said inlets.

1 4. The method as recited in claim 3 further comprising the step of applying a
2 reenterable seal to flow channels in said package.

1 5. The method as recited in claim 1 wherein said substrate comprises alignment
2 marks for forming said probe arrays thereon in a desired position, and wherein said
3 alignment marks are used to identify locations for said separating of said substrate into chips.

1 6. The method as recited in claim 1 wherein said package comprises an
2 alignment structure thereon, wherein said step of mating said chip to said package uses said
3 alignment structures to position said package at a desired position.

1 7. The method as recited in claim 1 wherein said package comprises an
2 alignment structure thereon, and further comprising the step of identifying the location of at
3 least one target on said probe array in a scanner, wherein said package is placed at a desired
4 location in said scanner using said alignment structure.

1 8. The method as recited in claim 1 wherein said step of forming a plurality of
2 probe arrays comprises the steps of:
3 selectively exposing said substrate to light;
4 coupling selected monomers to said substrate where said substrate has been exposed
5 to light.

1 9. The method as recited in claim 1 wherein said step of separating comprises
2 the steps of:
3 scribing said substrate in desired locations;
4 breaking said substrate along said scribe lines.

1 10. The method as recited in claim 1 wherein said step of forming a plurality of
2 probe arrays on said substrate is a step of forming a plurality of oligonucleotide probe arrays
3 on said substrate.

1 11. The method as recited in claim 10 further comprising the steps of flowing
2 labeled oligonucleotide target molecules through said reaction chamber and identifying
3 where said target molecules have bound to said substrate.

1 12. The method as recited in claim 11 wherein said package comprises a
2 temperature probe and further comprising the step of monitoring and adjusting a temperature
3 in said reaction chamber.

1 13. The method as recited in claim 1 wherein said package is formed by the steps
2 of:
3 forming first and second package portions; and
4 acoustically welding said first and second package portions together.

1 14. The method as recited in claim 1 wherein said step of mating said chips to
2 packages comprises the step of binding said chips to said package with an adhesive.

1 15. The method as recited in claim 14 wherein said packages comprise a recessed
2 region thereon, whereby said chips do not extend above a surface of said packages.

1 16. The method as recited in claim 1 further comprising the step of flowing target
2 molecules through said reaction chamber.

1 17. An apparatus for packaging a substrate, said apparatus comprising:
2 a substrate having a first surface and a second surface, said first surface comprising a
3 probe array;
4 a body having a mounting surface with a fluid cavity, said second surface attached to
5 said cavity; and
6 a cover attached to said mounting surface for sealing said cavity.

1 18. The apparatus of claim 17 wherein said cavity comprises an inlet port and an
2 outlet port, said inlet and outlet ports permitting fluids to circulate into and through said
3 cavity.

1 19. The apparatus of claim 18 wherein said inlet and outlet ports comprise a
2 reenterable seal.

1 20. The apparatus of claim 17 wherein said probe array comprises an array of
2 oligonucleotide probes.

1 21. An apparatus for packaging a substrate, said apparatus comprising:
2 a substrate having a first surface and a second surface, said first surface comprising a
3 probe array and said second surface being an outer periphery of said first surface;
4 a body having a mounting surface, an upper surface, and a cavity bounded by said
5 mounting surface and said upper surface, said second surface being attached to said cavity
6 and said first surface being within said cavity; and
7 a cover attached to said mounting surface for defining an upper boundary to said
8 cavity;
9 wherein said cavity comprises a diffuser and a concentrator, said diffuser and said
10 concentrator permitting laminar fluid flow through said cavity.

1 22. The apparatus of claim 21 wherein said probe array comprises an array of
2 oligonucleotide probes.

1 23. The apparatus of claim 21 wherein said cover comprises a depression for
2 receiving a temperature control element to-maintain a reaction temperature in said cavity.

1 24. The apparatus of claim 21 wherein said cover comprises a first half mated to a
2 second half.

1 25. The apparatus of claim 24 wherein said first half comprises a first channel and
2 a second channel, said first channel being in fluid communication with said diffuser and said
3 second channel being in fluid communication with said concentrator.

1 26. The apparatus of claim 25 wherein said second half comprises a third channel
2 and a fourth channel, said third channel being in fluid communication with said first channel,
3 and said fourth channel being in fluid communication with said second channel. .

1 27. The apparatus of claim 26 wherein said first channel and said second channel
2 comprise re-enterable seals for sealing fluid in said cavity.

1 28. An apparatus for mixing a fluid, the apparatus comprising:
2 a first substrate comprising a first inner surface functionalized with a microarray of
3 reactive moieties;
4 a substantially parallel second substrate also comprising a second inner surface,
5 wherein said first and second inner surfaces bound a closed chamber there between, said
6 chamber adapted to retain a quantity of fluid so that the fluid is in contact with both surfaces;
7 at least one bubble disposed within said chamber; and
8 means for moving the chamber so that the bubble moves relative to the fluid to effect
9 mixing of the fluid.

1 29. An apparatus for mixing a fluid, the apparatus comprising:
2 a first substrate comprising a first inner surface functionalized with a microarray of
3 reactive moieties;
4 a substantially parallel second substrate also comprising a second inner surface,
5 wherein said first and second inner surfaces bound a closed chamber there between, said
6 chamber adapted to retain a quantity of fluid so that the fluid is in contact with both surfaces;
7 at least one bubble disposed within said chamber, wherein said bubble is a magnetic

- 8 particle; and
- 9 means for moving the bubble relative to the fluid to effect mixing of the fluid.
- 1 30. The apparatus of claim 28, wherein the closed chamber has a thickness of less
2 than about 2 millimeters.
- 1 31. The apparatus of claim 29, wherein the closed chamber has a thickness of less
2 than about 2 millimeters.
- 1 32. The apparatus of claim 28, wherein both inner surfaces are functionalized with
2 reactive moieties.
- 1 33. The apparatus of claim 29, wherein both inner surfaces are functionalized with
2 reactive moieties.
- 1 34. The apparatus of claim 28, wherein the bubble comprises a gas.
- 1 35. The apparatus of claim 28, wherein the bubble comprises nitrogen.
- 1 36. The apparatus of claim 29, wherein said magnetic particle is a magnetic bead.
- 1 37. The apparatus of claim 28, wherein the bubble is produced by introducing a
2 volume of the fluid that is less than the total volume of the closed chamber.
- 1 38. The apparatus of claim 28, further including a flexible seal between the inner
2 surface of the first substrate and the inner surface of the second substrate.
- 1 39. The apparatus of claim 38, wherein said flexible seal includes a gasket.
- 1 40. The apparatus of claim 29, further including a flexible seal between the inner
2 surface of the first substrate and the inner surface of the second substrate.
- 1 41. The apparatus of claim 40, wherein said flexible seal includes a gasket.
- 1 42. The apparatus of claim 28, further comprising means for introducing fluid into
2 the closed chamber.
- 1 43. The apparatus of claim 29, further comprising means for introducing fluid into
2 the closed chamber.
- 1 44. The apparatus of claim 28, wherein the first substrate and the second substrate
2 are individually comprised of a material selected from the group consisting of glass, silicon,
3 fused silica, plastic, and a combination thereof.
- 1 45. The apparatus of claim 29, wherein the first substrate and the second substrate
2 are individually comprised of a material selected from the group consisting of glass, silicon,
3 fused silica, plastic, and a combination thereof.

- 1 46. The apparatus of claim 28, wherein the first substrate is comprised of glass.
- 1 47. The apparatus of claim 29, wherein the first substrate is comprised of glass.
- 1 48. The apparatus of claim 28, wherein the means for moving the bubble is selected
2 from the group consisting of rotating the apparatus about an axis, rolling the apparatus, and
3 reciprocally shaking the apparatus.
- 1 49. A method for mixing a fluid, comprising:
2 providing an apparatus according to claim 28;
3 introducing a fluid into the closed chamber;
4 introducing a bubble within the fluid; and
5 moving the bubble in the fluid to effect mixing of the fluid.
- 1 50. A method for mixing a fluid, comprising:
2 providing an apparatus according to claim 29;
3 introducing a fluid into the closed chamber;
4 introducing a bubble within the fluid; and
5 moving the bubble in the fluid to effect mixing of the fluid.
- 1 51. A method for mixing a fluid, comprising:
2 providing an apparatus according to claim 30;
3 introducing a fluid into the closed chamber,
4 introducing a bubble within the fluid; and
5 moving the bubble in the fluid to effect mixing of the fluid.
- 1 52. A method for mixing a fluid, comprising:
2 providing an apparatus according to claim 31;
3 introducing a fluid into the closed chamber;
4 introducing a bubble within the fluid; and
5 moving the bubble in the fluid to effect mixing of the fluid.
- 1 53. A method for mixing a fluid, comprising:
2 providing an apparatus according to claim 36;
3 introducing a fluid into the closed chamber;
4 introducing a bubble within the fluid; and
5 moving the bubble in the fluid to effect mixing of the fluid.

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1 54. A method for mixing a fluid, comprising:

2 providing an apparatus according to claim 48;

3 introducing a fluid into the closed chamber;

4 introducing a bubble within the fluid; and

5 moving the bubble in the fluid to effect mixing of the fluid.

1 55. An apparatus for mixing a fluid, comprising:

2 a first substrate and a second substrate having inner surfaces that define a closed

3 chamber therebetween, said chamber adapted to retain a quantity of fluid so that the fluid is
4 in contact with both inner surfaces;

5 means for creating bubbles in the fluid within the apparatus, whereby each bubble

6 displaces the fluid resulting in mixing; and

7 means for moving a bubble in the fluid.

1 56. The apparatus of claim 55, wherein the first substrate comprises a material

2 selected from the group consisting of glass, silicon, fused silica, and plastic.

1 57. An apparatus for mixing a fluid, comprising:

2 a first substrate and a substantially parallel second substrate having inner surfaces that

3 define a closed chamber therebetween, said chamber adapted to retain a quantity of fluid so
4 that the fluid is in contact with both inner surfaces;

5 means for providing bubbles in the fluid within the apparatus, whereby each said

6 bubble displaces the fluid resulting in mixing; and

7 means for moving a bubble in the fluid.

1 58. An apparatus for mixing a fluid, comprising:

2 a first substrate and a second substrate having inner surfaces that define a closed

3 chamber therebetween, said chamber adapted to retain a quantity of fluid so that the fluid is
4 in contact with both inner surfaces; and

5 means for creating bubbles in the fluid at selected locations within the apparatus,

6 whereby each bubble displaces the fluid resulting in mixing; and wherein at least one of said

7 inner surfaces is functionalized with reactive moieties.

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1 59. The apparatus of claim 58 wherein the reactive moieties comprise monomeric
2 species covalently bound to said inner surface, each of the monomeric species having at least
3 one reactive site.

1 60. The apparatus of claim 59 wherein the monomeric species are nucleotides.

1 61. The apparatus of claim 60 wherein the monomeric species are amino acids.

1 62. The apparatus of claim 61 wherein the reactive moieties comprise reactive sites
2 of monomeric species present at the terminus of a surface-bound polymer.

1 63. The apparatus of claim 62 wherein the surface-bound polymer comprises a
2 polynucleotide.

1 64. The apparatus of claim 62 wherein the surface-bound polymer comprises a
2 polyribonucleotide.

1 65. The apparatus of claim 64, wherein the surface-bound polymer comprises a
2 polypeptide.

1 66. A method comprising:

2 providing a first substrate and a second substrate having inner surfaces that define a
3 closed chamber therebetween, said chamber adapted to retain a quantity of fluid so that the
4 fluid is in contact with both inner surfaces, and wherein at least one of said inner surfaces is
5 functionalized with polynucleotides, polypeptides, or polysaccharides;

6 introducing a fluid containing a plurality of components into the closed chamber so as
7 to provide a quantity of fluid therein in contact with both inner surfaces;

8 providing a bubble in the fluid; and

9 moving a bubble within the fluid to result in mixing.

1 67. A method according to claim 66, wherein the polynucleotide is a
2 polyribonucleotide.

1 68. A method according to claim 66, wherein the chamber is adapted to retain a film
2 of fluid in contact with both inner surfaces.

1 69. A method according to claim 66 wherein the inner surfaces of the first and
2 second substrates are substantially parallel.

1 70. A method according to claim 66, wherein the chamber is less than two
2 millimeters in thickness.

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1 71. A method according to claim 66 further including using heat for said mixing.

1 72. A method according to claim 66 further including using ultrasonic radiation for
2 said mixing.

1 73. A method of claim 66, wherein the at least one of said inner surfaces is
2 functionalized with polynucleotides.

1 74. A method of 66, wherein the at least one of said inner surfaces is functionalized
2 with polypeptides.

1 75. A method comprising:

2 providing a first substrate and a second substrate having inner surfaces that define a
3 closed chamber therebetween, said chamber adapted to retain a quantity of fluid so that the
4 fluid is in contact with both inner surfaces, and wherein at least one of said inner surfaces is
5 functionalized with an array of RNA or DNA probes;

6 introducing a fluid sample containing DNA or RNA into the closed chamber so as to
7 provide a quantity of fluid therein in contact with both inner surfaces;

8 providing a bubble in the fluid;

9 moving a bubble within the fluid to result in mixing;

10 after hybridization is complete, removing the sample from the apparatus; and

11 analyzing the functionalized inner surface for DNA or RNA that has hybridized.

1 76. A method according to claim 75 additionally comprising heating the DNA or
2 RNA containing sample fluid while in the closed chamber.

1 77. A method according to claim 76 additionally comprising washing the
2 functionalized inner surface prior to the analyzing.

1 78. A method according to claim 75, wherein the bubble is moved in a circular
2 pattern.

1 79. A method according to claim 78, wherein the bubble is moved in the circular
2 pattern that includes exiting the closed chamber.

1 80. A method comprising:

2 providing a first substrate and a second substrate having inner surfaces that define a
3 closed chamber therebetween, said chamber adapted to retain a quantity of fluid so that the
4 fluid is in contact with both inner surfaces, and wherein at least one of said inner surfaces is
5 functionalized with an immobilized biological polymer;

6 introducing a fluid containing a plurality of components into the closed chamber so as
7 to provide a quantity of fluid therein in contact with both inner surfaces;
8 providing a bubble in the fluid; and
9 moving a bubble within the fluid to result in mixing.

1 81. A method according to claim 80, wherein said biological polymer includes a
2 polynucleotide.

1 82. A method according to claim 81, wherein said polynucleotide is a
2 polyribonucleotide.

1 83. A method according to claim 80, wherein said biological polymer includes
2 polypeptides.

1 84. A method according to claim 80, wherein said biological polymer includes
2 polysaccharides.

1 85. A method for mixing a film of fluid, comprising:
2 providing a first substrate and a substantially parallel second substrate having inner
3 surfaces that define a closed chamber therebetween, said chamber adapted to retain a quantity
4 of fluid so that the fluid is in contact with both inner surfaces;
5 introducing a fluid containing a plurality of components into the closed chamber so as
6 to provide a film of fluid therein; and
7 nucleating a bubble within the film of fluid, whereby, as the bubble is nucleated and
8 dispelled, the fluid is displaced resulting in mixing.

1 86. The method of claim 85, wherein the dispelling comprises moving the bubble.

1 87. An apparatus for mixing a fluid, comprising:
2 a first substrate and a second substrate having inner surfaces that define a closed
3 chamber therebetween, said chamber adapted to retain a quantity of fluid so that the fluid is
4 in contact with both inner surfaces;
5 means for nucleating bubbles in the fluid comprising discrete sources for creating
6 individual bubbles at selected locations within the apparatus, whereby, as each bubble is
7 nucleated and dispelled, the fluid is displaced resulting in mixing; and
8 means for moving a bubble in the fluid.

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